38. The method according to claim 23, wherein the activity of the signal transduction system of cells is a change in intracellular concentrations of responding substances selected from the group consisting of cAMP, inositol phosphate and calcium ion.--

add 37

REMARKS

In the above referenced application, claims 14, 16-19, 21-24 and 26 are pending in the above referenced application and stand rejected. Claims 14, 16, 17, 19, 21, 22-24 have been amended to more particularly set forth and distinctly claim the present invention. Support for the amendments is found throughout the specification. In addition, new claims 27-38 have been added. Claim 27 is directed to the method described in the specification in the Examples. Claims 28-38 recite that the activity is a change in intracellular concentrations of responding substances selected from the group consisting of cAMP, inositol phosphate and calcium ion. These claims are supported in specification, e.g., page 18, lines 23-26 and therefore do not add new matter. In light of the above amendments and following discussion, Applicant respectfully requests that the outstanding rejections be withdrawn and the claims be allowed.

A petition for an extension of time of one (1) month for responding to the outstanding Office Action and the appropriate fee authorization is enclosed herewith.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are entitled "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

Claims 14, 16-19, 21-24 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite. It is the Examiner's position that claims 14, 16, 17, and 24 are incomplete method claims. Claims 19 and 23 are also deemed indefinite. While applicants do not agree with the Examiner's position, in order to expedite prosecution, the claims have been amended, e.g., to include a step wherein the

operation activity of the aberrant receptor in the presence of the substance is compared with the operation activity of the aberrant receptor in the absence of the substance, wherein a change in the operation activity of the aberrant receptor indicates that the substance causes the aberrant receptor to operate in a manner similar to the non-aberrant receptor. In view of these amendments, Applicant respectfully requests the rejections to be reconsidered and withdrawn.

Claims 14, 16-19, 24 and 26 stand rejected under 35 U.S.C. 102(b) as being anticipated by Birnbaumer et al., Molecular Endocrinology 8(7):886-894, 1994. Applicant respectfully traverses this rejection.

Applicant respectfully submits that this reference fails to anticipate the present claims. For a reference to anticipate a claim it must teach each and every element of the claim. Birnbaumer teaches a mutation in the ligand binding region of type-2 vasopressin receptor that is responsible for X-linked congenital nephrogenic diabetes insipidus (CNDI). As stated in the Abstract, the study described therein sought to determine whether the mutation accounts for the CNDI phenotype. The Examiner cites the reference as teaching that AVP (arginine vasopressin), the natural ligand, stimulated the mutant receptor with an EC_{50} that was increased over wild-type by about 60-fold. The Examiner cites this as meeting the limitation of screening for a substance that would operate the receptor in a manner similar to the wild-type receptor.

Applicant respectfully submits that Birnbaumer fails to teach every element of the claims. The present claims are directed to, e.g., a method of screening substances for a substance capable of causing an aberrant receptor, which has substantially changed affinity for substances that have a natural affinity for a non-aberrant receptor, to operate in a manner similar to the non-aberrant receptor comprising: 1) bringing the aberrant receptor into contact with a subject substance, 2) assaying the operation activity of said substance on said receptor and 3) comparing the operation activity of the aberrant receptor in (2) with the operation activity of the aberrant receptor without the substance, wherein a change in the operation activity of the aberrant receptor indicates that the substance causes the aberrant receptor to operate

in a manner similar to the non-aberrant receptor. The methods of the present invention are not used to screen for a natural ligand, e.g., AVP. In fact, the aberrant receptor in the present invention has a substantially changed affinity for substances that have a natural affinity for a non-aberrant receptor, i.e., the natural ligand. The methods in the present claims are used to find substances, e.g., agonists, that cause the aberrant receptor to operate like the non-aberrant receptor. Birnbaumer fails to teach any method in which the aberrant receptor is brought into contact with a subject substance, the operation activity of said substance on said receptor is assayed and the operation activity of the aberrant receptor in the presence of the substance is compared with the operation activity of the aberrant receptor without the substance, wherein a change in the operation activity of the aberrant receptor indicates that the substance causes the aberrant receptor to operate in a manner similar to the non-aberrant receptor. Thus, Birnbaumer fails to anticipate the claims of the present invention. In addition, for the reasons stated above, new claims 27-38 are also not anticipated by Birnbaumer.

Applicant therefore respectfully requests reconsideration and withdrawal of this rejection.

Claim 14 stands rejected under 35 U.S.C. 102(b) as being anticipated by Green et al., J. Biol. Chem, 268(31):23116-23121, 11/5/93. Applicant respectfully traverses this rejection.

Applicant respectfully submits that this reference fails to anticipate claim 14. Green et al. as discloses a human β_2-adrenergic receptor with lowered binding affinity for epinephrine as compared to wild type. The Examiner cites Green et al. as teaching that they screened for, but were not able to find, substances that would operate the receptor in a similar manner to the non-aberrant receptor, citing the sentence bridging pages 23120-23121. Applicant disagrees with the Examiner's interpretation of Green.

Green fails to teach a method of screening substances for a substance capable of causing the aberrant receptor to operate in manner similar to the non-aberrant receptor as claimed. Green et al. were using agonist binding studies to attempt to

detect a high affinity binding site in the mutant. They were unable to do so. Similarly, in adenyl cyclase assays, the impaired physical coupling of the receptor with an agonist resulted in significantly depressed agonist stimulated activity. Thus, Green et al. were not using the mutant to screen for compounds that function to restore the operation activity of the aberrant receptor to that of the wild-type receptor, as described in the present application. Rather, Green was seeking to further characterize the mutant receptor.

Clearly, Green et al fail to teach every element, i.e., step, of the presently claimed method. Thus, Green et al. fail to anticipate claim 14. Applicant therefore respectfully requests reconsideration and withdrawal of this rejection.

Claim 14 stands rejected under 35 U.S.C. 102(b) as being anticipated by Kong et al., J. Biol. Chem. 268(31):23055-23058, 1993. Applicant respectfully traverses this rejection.

Applicant respectfully submits that this reference fails to anticipate claim 14. Kong et al. teaches a mutated δ opioid receptor (D95N) in which the aspartic acid 95 has been substituted with an asparagine. D95N has reduced affinity for δ receptor-selective agonists such as enkephalin, and for non-peptide agonists. In contrast, δ receptor-selective antagonists bound equally well to wild type and mutant receptors. Also, non-selective opioid agonists bound equally well. Thus, Kong et al. teaches affinity studies used to determine the binding characteristics of the mutant receptor. It fails to teach the elements of the presently claimed methods.

The Examiner cites Kong as teaching assays consistent with claim 14 (referring to Fig. 2 and Table I), and showing that non-selective agonists were able to "operate" the receptor in a manner "similar to non-aberrant receptor." Applicant disagrees with the Examiner's interpretation of Kong. Kong is concerned with identifying the key residue involved in selective agonist binding to the δ opioid receptor. Kong simply fails to teach <u>any</u> method of screening substances for a substance capable of causing an aberrant receptor, which has substantially changed affinity for substances that have a natural affinity for a non-aberrant receptor, to operate in a manner similar to the non-

aberrant receptor, in which the aberrant receptor is brought into contact with a subject substance, the operation activity of said substance on said receptor is assayed and the operation activity of the aberrant receptor in the presence of the substance is compared with the operation activity of the aberrant receptor without the substance, wherein a change in the operation activity of the aberrant receptor indicates that the substance causes the aberrant receptor to operate in a manner similar to the non-aberrant receptor. Thus, Kong fails to anticipate the claims of the present invention. Applicant therefore respectfully requests reconsideration and withdrawal of this rejection.

Claims 14, 16-19, 21-24 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lebrun et al., J. Biol. Chem. 268(15):11272-11277, 5/25/93, previously of record, in view of Choong et al., J. Clin. Endocrinol. Metab. 81(1):236-243, 1996. Applicant respectfully traverses this rejection.

Lebrun teaches the use of two monoclonal antibodies to study mutant insulin receptor kinase activity. The mutation in the insulin receptor does not affect hormone binding, but rather impairs the ability of insulin, once bound, to stimulate the receptor kinase. The receptor kinase is functional. Lebrun was interested in finding a link in the defect of insulin dependant activation of the receptor tyrosine kinase and structural modifications of the Mutant Insulin Receptor Val^{382}. To do this, they studied the interaction of the receptors with antibodies to the extracellular domain. Contrary to the Examiner's statements in the Office Action, Lebrun does not teach a method of screening for substances, i.e., antibodies, that restore the operation activity of the aberrant receptor. Rather, Lebrun teaches that the antibodies induce a conformational change in the mutant receptor, which is not normally changed by insulin binding. The type of mutation in Lebrun is very different from the aberrant receptor used in the presently claimed methods, which has substantially changed affinity for substances that have a natural affinity for a non-aberrant receptor, e.g., natural ligands. Furthermore, the methods used in Lebrun are different from the methods presently claimed.

In fact, the Examiner agrees that Lebrun is different from the methods of the claims and specifically that the receptor mutation was not in the extracellular, ligand binding portion of the receptor, and that no pharmaceutical composition was prepared.

There is simply no teaching, suggestion or motivation to use the disclosure of Lebrun to develop a method of screening substances for a substance capable of causing an aberrant receptor, which has substantially changed affinity for substances that have a natural affinity for a non-aberrant receptor, to operate in a manner similar to the non-aberrant receptor, as presently claimed. The goals of Lebrun are simply different from the purpose of the present methods.

The Examiner must therefore provide a secondary reference which provides the teachings, suggestions or motivation that are missing from Lebrun. The Examiner has failed to do so.

Choong et al. teaches the study of a mutation in the androgen receptor (AR) which results in reduced ligand binding affinity and reduced AR messenger RNA levels in genital skin fibroblasts. The mutation was found to be in the carboxy terminal region of the ligand binding domain and the studies show that this region is important for normal AR function and gene expression. There is simply no teaching, suggestion, or motivation to use either the receptor, or any of the methods described in Choong to develop a method of screening for substances capable of causing an aberrant receptor, which has substantially changed affinity for substances that have a natural affinity for a non-aberrant receptor, to operate in a manner similar to the non-aberrant receptor as presently claimed.

It is the Examiner's position that it would have been obvious to substitute the mutated androgen receptor (AR) of Choong et al. in the method of Lebrun et al. for the purpose of finding an antibody that would compensate for the AR mutation described by Choong et al. Applicant respectfully submits that Choong fails to make up for the deficiencies of Lebrun. As aforesaid, Choong teaches a study that determined that a mutation in the carboxyl-terminal region of the ligand binding domain of AR that is

associated with reduced ligand binding and reduced AR mRNA levels. It fails to teach the methods of screening compounds presently claimed. There is simply no motivation for one of ordinary skill in the art to combine Choong with Lebrun to obtain the methods of the present invention. Even if the referenced were combined they clearly would not make the methods of the present invention obvious to one of ordinary skill in the art.

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See MPEP 2143.01; *In re Fine*, 837 F. 2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F. 2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). The Lebrun and Choong references cited, alone or in combination, include no such teaching, suggestion or motivation. One of ordinary skill in the art would simply have no motivation to combine the references. And, even if the referenced were combined, the present methods would simply not have been obvious there from. The Examiner is using impermissible hindsight to combine the references. Thus, the Examiner has failed to establish a *prima facie* case of obviousness. Applicants therefore respectfully request reconsideration and withdrawal of this rejection.

In addition, new claims 27-38 are not anticipated or obvious over the cited references. For example, the Androgen Receptor of Choong et al. is a nuclear receptor and function by producing a transcription factor after androgen binds to it. It does not change intracellular concentrations of responding substances selected from the group consisting of cAMP, inositol phosphate and calcium ion, as claimed in claims 28-38. Therefore, the methods of the new claims are not obvious from the cited references.

In view of the discussion above, it is respectfully submitted that the present application is in condition for allowance. An early reconsideration and notice of allowance are earnestly solicited. Should the Examiner wish to discuss the above amendment made herein, the undersigned attorney would appreciate the opportunity

to do so. Thus the Examiner is hereby invited to call the undersigned, collect at the number shown below.

Respectfully submitted,

Date: October 18, 2001

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Please amend the claims as follows:

14. (three times amended) A method of screening substances for a substance capable of causing an aberrant receptor, which has substantially changed affinity for substances that have a natural affinity for a non-aberrant receptor, to operate in a manner similar to the ~~a~~ non-aberrant receptor comprising:

1) bringing ~~an~~ the aberrant receptor into contact with a subject substance,

2) ~~and~~ assaying the operation activity of said substance on said receptor and

3) comparing the operation activity of the aberrant receptor in (2) with the operation activity of the aberrant receptor without the substance,

wherein a change in the operation activity of the aberrant receptor indicates that the substance causes the aberrant receptor to operate in a manner similar to the non-aberrant receptor.

16. (three times amended) A method of screening substances for a substance for treatment of a disease in a mammal caused by an aberrant receptor, which has substantially changed affinity for substances that have a natural affinity for a non-aberrant receptor, comprising:

1) bringing ~~an~~ the aberrant receptor into contact with a substance, ~~and~~

2) assaying the operation activity of said substance on said receptor,

3) comparing the operation activity of the aberrant receptor in (2) with the operation activity of the aberrant receptor without the substance, and

4) selecting a substance that causes the aberrant receptor to operate in a manner similar to the non-aberrant receptor, wherein the substance can be used to treat a disease caused by the aberrant receptor.

17. (twice amended) A method of screening for a drug for restoring normal function to a signal transduction system of a cell having an aberrant receptor of a mammal suffering from a disease caused by the aberrant receptor which affects the signal transduction system of the cell, which comprises:

1) bringing the aberrant receptor into contact with a subject substance, ~~and~~

2) assaying the activity of said substance on said receptor,

3) comparing the operation activity of the aberrant receptor in (2) with the operation activity of the aberrant receptor without the substance, and

4) selecting a substance that causes the aberrant receptor to operate in a manner similar to the non-aberrant receptor, ~~and~~ wherein the activity is an activity that restores the normal function of the cell.

19. (twice amended) The screening method according to claim 16, wherein the aberrant receptor is encoded by a gene in the mammal, the method further ~~comprises~~ comprising the step of selecting the receptor by comparing the gene encoding the aberrant receptor, isolated from a cell of a the mammal ~~suffering from a disease caused by the aberrant receptor~~, with a gene encoding the non-aberrant receptor, prepared from a cell of a mammal of the same species that does not carry the aberrant receptor.

21. (twice amended) A method of preparing a substance for treatment of a disease in a mammal caused by an aberrant receptor having a substantially changed affinity for substances, which results in the substantial reduction in activity of the signal transduction system of cells having the aberrant receptor, the method comprising:

~~selecting a substance from subject substances by~~ bringing the aberrant receptor into contact with a subject substance,

assaying the activity of said substance on the aberrant receptor,

selecting a substance that substantially operates the signal transduction system of the cell having the aberrant receptor wherein said activity is activity that restores wide-type activity of the receptor

and admixing the selected substance with a pharmaceutically acceptable carrier.

22. (three times amended) The method according to claim 21, wherein the aberrant receptor, which has substantially changed affinity for substances, is

encoded by a gene in the mammal and is isolated from a cell which expresses ~~with~~ the gene encoding the aberrant receptor.

23. (three ~~times~~ amended) The method according to claim 22, wherein the gene encoding the aberrant receptor is selected by comparing the gene encoding the aberrant receptor, prepared from a cell of ~~a~~ the mammal ~~suffering from a disease caused by the aberrant receptor~~, with a gene encoding the non-aberrant receptor, prepared from a cell of a mammal of the same species that does not carry the aberrant receptor.

24. (three times amended) A method of screening for a substance capable of causing an aberrant receptor, which has substantially changed affinity for substances, to operate in a manner similar to a non-aberrant receptor comprising:

(4) expressing in a cell the gene encoding the aberrant receptor,

(5) isolating the aberrant receptor from the cell,

(6) providing a substance to the aberrant receptor ~~and~~,

(4) determining the operation activity of ~~said~~ the substance on ~~said~~ the receptor, and

(5) comparing the operation activity of the aberrant receptor in (4) with the operation activity of the non-aberrant receptor,

wherein a similar operation activity in (4) to the operation activity of the non-aberrant receptor indicates that the substance causes the aberrant receptor to operate in a manner similar to the non-aberrant receptor.

Please add the following new claims:

-- 27. A method of screening for a substance capable of causing an aberrant receptor, which has substantially changed affinity for substances, to operate in a manner similar to a non-aberrant receptor comprising:

(1) providing cells expressing the gene encoding the aberrant receptor,

(2) providing the substance to be screened to the cells expressing the aberrant receptor,

(4) determining the operation activity of said substance on said receptor, and

(4) comparing the operation activity of the aberrant receptor with the operation activity of the non-aberrant receptor, wherein a change in the operation activity of the aberrant receptor indicates that the substance causes the aberrant receptor to operate .

28. The method according to claim 14, wherein the operation activity is a change in intracellular concentrations of responding substances selected from the group consisting of cAMP, inositol phosphate and calcium ion.

29. The method according to claim 16, wherein the operation activity is a change in intracellular concentrations of responding substances selected from the group consisting of camp, inositol phosphate and calcium ion.

30. The method according to claim 17, wherein the operation activity is a change in intracellular concentrations of responding substances selected from the group consisting of camp, inositol phosphate and calcium ion.

31. The method according to claim 18, wherein the operation activity is a change in intracellular concentrations of responding substances selected from the group consisting of camp, inositol phosphate and calcium ion.

32. The method according to claim 19, wherein the operation activity is a change in intracellular concentrations of responding substances selected from the group consisting of camp, inositol phosphate and calcium ion.

33. The method according to claim 24, wherein the operation activity is a change in intracellular concentrations of responding substances selected from the group consisting of camp, inositol phosphate and calcium ion.

34. The method according to claim 26, wherein the operation activity is a change in intracellular concentrations of responding substances selected from the group consisting of camp, inositol phosphate and calcium ion.

35. The method according to claim 27, wherein the operation activity is a change in intracellular concentrations of responding substances selected from the group consisting of camp, inositol phosphate and calcium ion.

36. The method according to claim 21, wherein the activity of the signal transduction system of cells is a change in intracellular concentrations of responding substances selected from the group consisting of cAMP, inositol phosphate and calcium ion.

37. The method according to claim 22, wherein the activity of the signal transduction system of cells is a change in intracellular concentrations of responding substances selected from the group consisting of cAMP, inositol phosphate and calcium ion.

38. The method according to claim 23, wherein the activity of the signal transduction system of cells is a change in intracellular concentrations of responding substances selected from the group consisting of cAMP, inositol phosphate and calcium ion.--